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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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<div>27476 7590 07/11/2007</div> <div>NOVARTIS VACCINES AND DIAGNOSTICS INC.</div> <div>CORPORATE INTELLECTUAL PROPERTY R338</div> <div>P.O. BOX 8097</div> <div>Emeryville, CA 94662-8097</div>				
			<div>EXAMINER</div> <div>RAGHU, GANAPATHIRAM</div>	
			<div>ART UNIT</div> <div>1652</div>	<div>PAPER NUMBER</div>
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/526,125

Applicant(s)

PIZZA ET AL.

Examiner

Ganapathirama Raghu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 May 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 and 11-15 is/are pending in the application.
- 4a) Of the above claim(s) 12-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-9 and 11 is/are rejected.
- 7) ☒ Claim(s) 4 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☒ Other: SEQ ALIGN.

DETAILED ACTION

Applicants' election without traverse of Group III, claims 1-9 and 11 and cancellation of claim 10 in the reply filed on 05/24/2007 is acknowledged.

Claims 1-9 and 11-15 are pending in this application. Claims 1-9 and 11 are under consideration for examination and claims 12-15 are being withdrawn as they are directed to non-elected inventions.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). This application claims the priority date of United Kingdom application 0220205.9 filed on 08/30/2002. The instant claims are granted the foreign priority date, as the disclosure contains the elected subject-matter.

Objection to the Abstract

The abstract of the disclosure is objected to: the Abstract should be on a separate sheet of paper. Correction is required. See MPEP § 608.01(b).

Specification Objections

The disclosure is objected to because of the following informalities:

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Appropriate correction is required.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c) as being in improper form, because a multiple dependent claim shall not serve as a basis for any other multiple dependent claim. Claim 4 depends on claims 1-3, and claim 3 which is a multiple dependent claim depending on claims 1 and 2. See MPEP § 608.01(n). Accordingly, claim 4 has not been further treated on the merits.

Claims 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 8 and 9 are not further limiting claim 1. Intended use statements have no patentable value. Appropriate correction is required.

Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the phrase "preferably Glu to Asp ...". The metes and bounds of the claim are not clear to the examiner, as it is unclear if the residue for the mutant enzyme must be Glu to Asp or not? Clarification and correction is required.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

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invention. Claim 7 recites the phrase "...wherein the fragment..." and is also dependent on claim 6 and claim 6 is not directed a protein comprising a fragment, therefore there is insufficient antecedent basis for this limitation in the claim and makes the claim confusing. Clarification and correction required.

Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 5-9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). However, the specification does not reasonably provide enablement for any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim.

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Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3, 5-9 and 11 are so broad as to encompass any mutant *Neisseria meningitidis* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant *Neisseria meningitidis* ADP-ribosylating enzymes, said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. In this

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case the disclosure is limited to an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). In view of the great breadth of the claims, the amount of experimentation required to determine a use for the full scope of the claims, i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given

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protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompasses any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The specification does not enable the full scope of claims 1-3, 5-9 and 11, because the specification does not establish: **(A)** mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, the structure of all polypeptides with desired activity i.e., reduced or eliminated ADP-ribosyltransferase activity and as an immunogen; **(B)** the general tolerance of the polypeptide to modification and extent of such tolerance; **(C)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and **(D)** the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides and encoding polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of

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enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Written Description

Claims 1-3, 5-9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5-9 and 11, as interpreted, are directed to a genus of polypeptides i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by

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structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, there is no structure correlated to associated function recited in claims with regard to the members of the genus polypeptides i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, as claimed in claims 1-3, 5-9 and 11. While the specification in the instant application discloses the structure, an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D), it fails to provide any information as to the structure associated with function

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for the genus of polypeptides claimed i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, with no structural limitations. The lack of description of any additional mutants from any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-9 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Masignani et al., (WO 02/079242 A2, publication date 10/10/2002) when given the broadest

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interpretation. Claims 1-3, 5-9 and 11 are directed to any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen or mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). Masignani et al., (*supra*) have disclosed a mutant *Neisseria meningitides* ADP-ribosylating enzyme comprising substitution of Glu-109 or Glu-111 or Glu-120 with Asp of *Neisseria meningitides* wild-type ADP-ribosylating enzyme of SEQ ID NO: 1 and use of said mutant ADP-ribosylating enzyme as an immunogen (pages 2-5 and especially Table 1 preferred site of mutations and replacement residue). Therefore the reference of Masignani et al., anticipates claims 1-3, 5-9 and 11 of the present invention.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

The teaching of the following reference is made of record. However, the reference is not used in any prior art rejections.

Tettelin et al., (Science, 2000, Vol. 287: 1809-1815) teach the isolation of a polypeptide from *Neissseria meningitidis* with 100% sequence homology to SEQ ID NO: 1, the wild-type enzyme of the instant application and same as the source of the enzyme that was used to generate

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mutant ADP-ribosylating enzyme. However, Tettelin et al., have not assigned any functional activity to the disclosed sequence.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

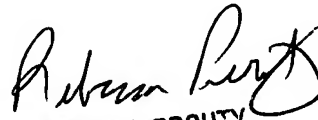
It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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June 25, 2007.


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